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Impact of productive and dry chronic cough on mortality in the Canadian Longitudinal Study on Aging (CLSA)

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Background: Chronic cough is a common troublesome condition and accounts for a high burden on quality of life. Previous data investigating the mortality associated with chronic cough has been derived in patients with chronic bronchitis. No data exists on chronic dry cough. Therefore, we investigated if chronic dry and productive cough is independently associated with increased mortality.

Methods: The Canadian Longitudinal Study on Ageing (CLSA) is a prospective, nationally generalizable, stratified random sample of adults aged 45–85 years at baseline recruited between 2011–2015 and followed up three years later. Chronic cough was identified based on a self-reported daily cough in the last 12 months. Deaths were confirmed by the Ministry of Health and/or completion of descendent questionnaire by a family member. Models were investigated for dry and productive chronic cough and was adjusted for age, sex, smoking, body mass index (BMI), and respiratory diseases.

Results: Of the 30,016 participants, 4,783 (15.9%) reported chronic cough at baseline; 2,724 (57%) had a dry cough, and 2,059 (43%) had productive chronic cough. There was a total of 561 deaths between baseline and follow-up-1 (3 years later). There was a 49% higher risk of death in participants with chronic productive cough {adjusted odds ratio (aOR) 1.49 [95% confidence intervals (CI): 1.08–2.07]}, but not dry chronic cough [aOR 0.85 (0.60–1.20)]. The effects of chronic productive cough on mortality were persistent in those with no airflow obstruction [chronic productive cough aOR 1.90 (1.09–3.31)].

Conclusions: Chronic productive cough is associated with a higher risk of death, while chronic dry cough has no impact on mortality risk of death in middle-aged and older adults. This highlights the importance of careful evaluation of patients with chronic cough.

Keywords: Chronic cough; mortality; epidemiology; Canadian Longitudinal Study on Ageing (CLSA)

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Introduction

Cough is the leading cause for ambulatory and primary care visits to physicians (1,2). Chronic cough is defined as a daily cough lasting greater than eight weeks affecting approximately 10% of the general population and is associated with significant impairment in quality of life (3-9). Chronic cough is also one of the most common reasons for referral to a specialist in secondary care, representing a significant burden on the health care system (10,11). Although these are predominantly dry chronic cough, approximately 25% have a productive chronic cough (12). Primary and secondary care physicians may consider this a benign condition with no substantial risk of death, but there is no data investigating the risk of death in patients with dry and productive chronic cough separately.

Prior to the introduction of effective anti-microbial therapy, deaths due to acute, sub-acute and chronic cough with sputum was commonly associated with pulmonary tuberculosis, pneumonia and other respiratory tract infections (13,14). However, after the world-wars, there was an increase in deaths following the mechanisation of coal mines (15,16). In December 1952, there was also a sharp increase in deaths in London (The Great Smog of London) with men dying with cough and sputum (17). This led the Medical Research Council (MRC) in the UK to setup the Bronchitis Research Committee led by Sir Charles Fletcher. This ultimately led to the MRC Chronic Bronchitis definition of cough which is productive sputum on most days for three months in two consecutive years (18).

Highlight box

Key findings

- There was a 49% higher risk of death in participants with chronic productive cough but not dry chronic cough. The effects of chronic productive cough on mortality were persistent in those with no airflow obstruction.

What is known and what is new?

- Previous data on mortality on chronic cough was extrapolated from data collected based on the Medical Research Council definition of chronic bronchitis. This new data examines the impact of both dry and productive chronic cough on mortality after adjusting for age, sex, smoking, body mass index, asthma and chronic obstructive pulmonary disease.

What is the implication, and what should change now?

- This highlights the importance of careful evaluation of the type of cough in patients with chronic cough.

Often forgotten is that the definition also required exclusion of other conditions associated with cough such as tuberculosis, bronchiectasis, pneumoconiosis and pulmonary oedema.

A number of cohort studies showed chronic bronchitis was associated with increased mortality in men, smokers, chronic obstructive pulmonary disease (COPD) and in those with lower lung function (19-26). However, these earlier studies had limitations as the focus was on the inclusion of participants with COPD, smokers, and use of occupational cohorts. Secondly, the definition of chronic bronchitis definition was typically synonymous with productive coughing during the winter months. Therefore, there is still an unmet need to understand the impact of chronic cough, both productive and dry, on mortality in a broad contemporary population from the general community beyond the 3-month seasonal definition.

The objective of this study was to estimate the impact of daily productive and dry chronic cough on the risk of death in a national sample of adults from the Canadian Longitudinal Study on Ageing (CLSA) who were between the ages of 45 and 85 years at baseline and followed up three years later. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-1306/rc>).

Methods

Study design and population

The CLSA is a large, nationally generalizable, stratified random sample of 51,338 Canadian men and women aged 45 to 85 years at baseline (recruited 2011–2015) from the 10 Canadian provinces (27). Eligible participants had to be physically and have cognitive capacity to participate independently and not live in institutions such as long-term care facilities. Participants were recruited in the tracking cohort (n=21,241) and the comprehensive cohort (n=30,097). Tracking cohort participants were randomly selected from the 10 provinces and completed interviews by phone. Participants in the comprehensive cohort were randomly selected from within 25–50 km of 11 data collection sites located in seven provinces (n=30,097). Participants in the comprehensive cohort completed in-depth questionnaires in person and physical assessments. Details on the study design have been described elsewhere (28). Each participant is followed every three years for 20 years or until death. The first follow-up was conducted between 2015 and 2018 with

a retention rate of 95%. The comprehensive data from baseline and first follow-up were included in the current analyses. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Hamilton Integrated Research Ethics Board and the CLSA scientific advisory board (Project ID: 1909024) and individual consent for this retrospective analysis was waived.

Chronic cough definitions

Participants who self-identified as having “daily cough over the last 12 months” were classified as having chronic cough at baseline. Chronic cough was further classified as a productive cough if participants reported “bringing up phlegm in the morning or most days during the year”. Participants who reported chronic cough without bringing up phlegm were categorized as having a dry cough.

Respiratory symptoms and chronic conditions

Self-reported presence of respiratory symptoms, including chest pain, shortness of breath upon exertion, and wheezing, were assessed. Participants were asked, “Do you wheeze with mild to moderate exertion? Do you become short of breath climbing stairs or walking up a small hill?” Disease definitions were based on self-reported physician diagnosis on direct questioning of participants by trained research assistants at baseline and follow-up. Participants were asked if they had ever been diagnosed with asthma, COPD or both by a physician. A history of infectious diseases such as pneumonia or influenza in the last 12 months was also surveyed.

Spirometry measurements

Lung function was measured with the TruFlow Easy-On Air Spirometer (nidd Medical Technologies, Switzerland) and categorized based on the American Thoracic Society requirements and criteria. Participants who screened positive for major contra-indications were excluded (21). The highest forced expiratory volume in 1 second (FEV₁) and FVC from 3 acceptable maximal efforts were selected. Only grades A and B were accepted for analysis. The FEV₁, FVC, and the ratio of FEV₁/FVC was recorded without bronchodilator therapy.

Chronic Airflow Obstruction (CAO) was defined as an FEV₁/FVC ratio of <0.7 as well as using the lower

limit of normal (LLN). Age, height, and sex were used to develop CLSA specific prediction reference values for this total population. These were based on standard allometric principles, FEV₁ and FVC increase in a positively accelerating manner with height ($y = k \times \text{Height}^{K_1}$). There was a proportionate increase in males relative to females at the same height ($y = k \times \text{Height}^{K_1} \times (1 + K_2 \times \text{Males}(1))$); and decreasing by a constant proportion with age ($y = k \times \text{Height}^{K_1} \times (1 + K_2 \times \text{Males}(1) \times (1 - K_3 \times (\text{Age})))$). Grade A and B spirometry data were available in 22,547 participants.

Mortality events

Deaths were confirmed by the Ministry of Health, Canada, in participants recruited at baseline but did not attend the follow-up 1 visit three years later. The exact date and cause of death were not made available by the Ministry of Health to maintain anonymity. Information about deaths were also collected from family members who completed a descendent questionnaire. Participants who had not died and did not attend for follow-up 1 were assumed to be alive.

Statistical analysis

The CLSA provides inflation weights and analytical weights, which were used for prevalence estimates and regression modelling respectively, that allow the results to reflect the population of Canada (28). As the exact date of death and withdrawal are missing, Logistic Regression (LR) models were used to estimate the odds ratios (OR) and 95% confidence intervals (95% CI) for the outcome of mortality. Potential confounding covariates associated with chronic cough and mortality were identified from prior literature describing associations, clinical relevance and mechanistic plausibility (19,29). The univariate association between each variable and mortality was assessed; a set of pre-defined variables were considered candidates for the model. Age and sex were automatically included in the model, and other potential covariates were added one at a time based on statistical significance. A model including age group (45–54, 55–64, 65–74, 75+ years), sex, smoking status (non-smoker, former smoker, and current smoker), body mass index (BMI) category (underweight, <18.5 kg/m²; normal weight, 18.5 to 24.9 kg/m²; overweight, 25.0–29.9 kg/m²; and obese >30 kg/m²). The presence of respiratory diseases including asthma, COPD, influenza and pneumonia in the past 12 months were included in the model. The model was performed for dry and productive chronic cough.

Table 1 Baseline demographics of participants who died

Variables	Subtypes	Deaths: no chronic cough		Deaths: dry chronic cough		Deaths: productive chronic cough	
		N	Weighted %	N	Weighted %	N	Weighted %
Deaths		419	1.22	55	1.22	85	3.27
Age category (years)	45–54	22	0.37	3	0.68	5	2.62
	55–64	69	0.92	6	0.45	17	2.08
	65–74	102	1.66	19	1.88	28	4.34
	75–85	226	4.84	27	3.69	35	5.44
Sex	Male	245	1.37	39	1.47	55	3.89
	Female	174	1.07	16	0.98	30	2.41
Body mass index	Under-weight	10	3.64	2	6.30	4	11.44
	Normal	121	1.25	13	0.80	15	1.99
	Overweight	153	1.01	17	1.42	30	3.15
	Obese	130	1.34	20	1.09	34	3.93
Smoking status	Current	49	2.25	8	0.96	27	3.81
	Previous	203	1.51	27	1.66	39	3.70
	Never	164	0.90	19	1.04	19	2.37

Demographics shown in those with no chronic cough, dry chronic cough and productive. Numbers and weighted % shown. Missing data for BMI (n=5) and smoking status (n=3).

Variables for which the deviance statistic was statistically significant (P value of <0.05) or those which impacted the strength of the association between chronic cough and mortality were kept in the model (30). Finally, the mutually adjusted model is presented along with 95% CI are shown.

As chronic cough and mortality are known to be associated with lower lung function, we also conducted subgroup stratified analyses in participants with or without airflow obstruction (FEV₁/FVC <0.7), and when the FEV₁% predicted is below or above 80% predicted. All statistical analyses were completed using SAS (Version 12.3).

Results

Study population

The comprehensive cohort included 30,097 participants. A total of 30,016 completed the chronic cough question at baseline. There were 967 participants who withdrew from the study after the baseline visit, and in 804 participants, there was missing data at the first follow-up who were assumed to be alive. Of the remaining, 4,783 (15.9%) participants reported chronic cough at baseline; 2,724 (57%) had a dry cough, and 2,059 (43%) had a productive chronic cough.

There was a total of 561 deaths between baseline and follow-up 1, which were confirmed by the Ministry of Health or by a family member completing the descendent questionnaire.

Baseline characteristics

The proportion of participants who died was highest in those with chronic productive cough (3.27%), with identical proportions with chronic dry cough (1.22%) and no chronic cough (1.22%) (Table 1). Participants with wheeze and shortness of breath on exertion, self-reported physician diagnosis of COPD, pneumonia or influenza in the last 12 months experienced a higher proportion of deaths (Table 2). The proportion of deaths was higher in those with productive chronic cough across all respiratory symptoms and diseases compared to those with dry chronic cough; however, the proportion of deaths in those with chronic dry cough was similar or lower compared with those without chronic cough.

Mortality

Chronic productive cough was independently associated with a 49% higher risk of death [adjusted OR (aOR) 1.49

Table 2 Respiratory co-morbidities of participants who died

Variables	Subtypes	Deaths: no chronic cough		Deaths: dry chronic cough		Deaths: productive chronic cough	
		N	Weighted %	N	Weighted %	N	Weighted %
Wheeze	No	343	1.16	40	1.39	40	2.50
	Yes	75	1.57	15	0.86	45	4.13
Shortness of breath up hill	No	398	1.15	53	1.25	70	3.01
	Yes	21	3.87	2	1.01	15	5.66
Chest pain	No	277	1.13	34	1.21	42	2.19
	Yes	75	0.92	10	0.95	23	4.02
Asthma only		30	0.90	3	0.91	7	2.79
COPD only		35	4.13	4	2.38	24	7.77
Asthma and COPD		15	3.87	5	2.46	6	2.50
No asthma or COPD		335	1.14	43	1.18	47	2.75
Pneumonia	No	394	1.16	51	1.23	73	3.17
	Yes	24	3.63	4	1.40	12	4.75
Influenza	No	388	1.20	52	1.29	73	3.11
	Yes	29	2.41	3	0.49	12	4.66
FEV ₁ /FVC	<0.7	52	2.47	10	2.05	13	2.18
	≥0.7	179	2.54	19	0.63	26	2.54
FEV ₁ % predicted	<80%	65	2.60	13	1.74	19	3.81
	≥80%	166	2.66	16	0.61	20	1.98

Data shown in those with no chronic cough, dry chronic cough and productive. COPD, obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

(95% CI: 1.08–2.07)], *Figure 1*], after adjusting for age, sex, smoking status, BMI, asthma, COPD, prior pneumonia and influenza. Chronic dry cough was not associated with a higher risk of death [aOR 0.85 (0.60–1.20), *Figure 1*] in the fully adjusted model.

Impaired lung function

The impact of chronic cough on mortality was stratified based on normal or low FEV₁% predicted and the presence of airflow obstruction (FEV₁/FVC <0.7). Mortality was also higher in participants with productive chronic cough and no airflow obstruction (FEV₁/FVC ≥0.7) compared with chronic dry cough [productive chronic cough OR 1.90 (1.09–3.31) *vs.* dry chronic cough adj OR 0.72 (0.41–1.28), *Table 3*]. There were no significant effects of chronic productive or dry chronic cough in patients with an FEV₁ <80% or ≥80% predicted (*Table 3*).

Discussion

To our knowledge, this is the first study to investigate the risk of death associated with dry and productive chronic cough in the general community over a 3-year period. Chronic productive cough was associated with an estimated 49% higher risk of death whilst chronic dry cough had no impact on the risk of death. Importantly, these associations were independent of other important risk factors and potential confounders including age, sex, smoking, low BMI, COPD, pneumonia and influenza. The effects of chronic productive cough on mortality persisted in those with no airflow obstruction.

The results of this study are difficult to directly compare with other studies because no studies have investigated chronic dry cough. Most studies have focused on chronic bronchitis, chronic mucus hypersecretion or coughing up phlegm in winter mornings. The most recent National Heart Lung and Blood Institute (NHLBI) pooled study

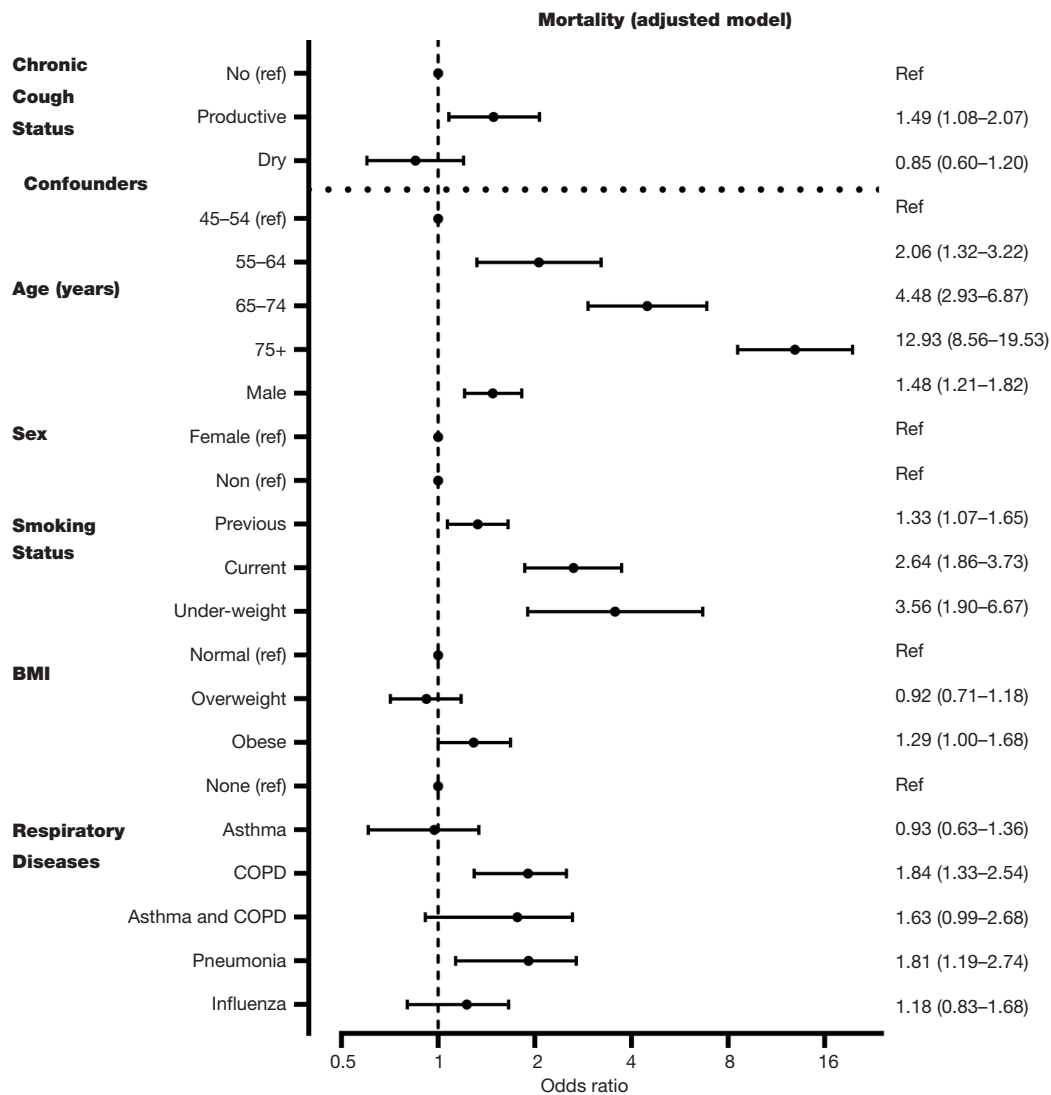


Figure 1 Mortality model for dry and productive cough. Data shown as estimated mean odds ratio and 95% CI and adjusted for age, sex, BMI, smoking status, respiratory diseases (asthma, COPD, influenza in the past 12 months, pneumonia in the past 12 months). BMI, body mass index; COPD, obstructive pulmonary disease.

Table 3 Fully adjusted mortality model stratified by FEV₁% predicted and airflow obstruction

Chronic cough status	FEV ₁ <80% pred (n=3,516)		FEV ₁ ≥80% pred (n=19,303)		FEV ₁ /FVC <0.7 (n=2,660)		FEV ₁ /FVC ≥0.7 (n=20,162)	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
No chronic cough	Ref		Ref		Ref		Ref	
Dry chronic cough	0.80	(0.40–1.63)	0.72	(0.39–1.34)	1.00	(0.47–2.13)	0.72	(0.41–1.28)
Productive chronic cough	1.14	(0.58–2.21)	1.72	(0.92–3.22)	0.85	(0.41–1.77)	1.90	(1.09–3.31)

Data shown as estimated mean odds ratio and 95% CI and adjusted for age, sex, BMI, smoking status, respiratory diseases (asthma, COPD, influenza in the past 12 months, pneumonia in the past 12 months). Number of participants for each category showed in brackets. FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OR, odds ratio; CI, confidence interval; BMI, body mass index; COPD, obstructive pulmonary disease.

of 9 cohorts of 22,235 recruited between 1971–2007 and followed-up for nearly 40 years, showed that non-obstructive chronic bronchitis was associated with a 50% increase in all-cause mortality in ever-smokers, but not in never smokers (31). A Danish study of over 100,000 randomly selected individuals from the community with a median follow-up of 9 years, showed a similar 34% increased risk of death in those presenting with chronic mucus hypersecretion, after adjusting for potential confounders (29). However, over 10,000 subjects with pre-existing asthma and COPD were excluded. The Tucson study recruited 1,412 subjects with normal spirometry between 1972–1973 and, after following for 30 years, also demonstrated a 31% increased risk of death with chronic bronchitis (32). Similar hazard ratios of death with chronic productive cough ranging between 1.23 to 1.56 have been reported in older cohort studies from Norway, UK, Poland, Oregon, and Paris (19,33–37). Whilst the estimated 49% increased risk of death with chronic productive cough in this study is consistent with previous data, it is also slightly disappointing. One might have hoped and expected an improvement in the risk of death over the last 40–50 years in developed countries. This raises broader questions about the need to provide better access and quality of health care, availability, compliance with medication, diagnosing and monitoring diseases, and primary and secondary prevention programmes which target high risk individuals at the population level.

Data from our mutually adjusted model (*Figure 1*) also reveals broader public health insights. The biggest modifiable risk factor for death is smoking established and propagated by Doll *et al.* (26). Our data shows that current smokers have a OR of 2.64, but for previous smokers the OR is 1.33, more than a 50% reduction. This underlines the importance of smoking cessation and public health measures to reduce its uptake. The banning of smoking in public spaces in Canada occurred between 1994 and 2006 with different regulations and timing across the provinces. However, all provinces had a public ban initiated before recruitment of the CLSA started. The long-term beneficial effects of this public smoking ban on chronic cough and mortality in the general community may take longer to detect, particularly as the CLSA recruited patients over the age of 45 who may have started or been exposed to smoking much earlier. The benefits of the public smoking ban also need to be balanced with the legalisation of vaping and cannabis in Canada since 2018. This requires further study in the context of the CLSA, which aims to follow patients for 20 years or death.

These findings also have important clinical implications for healthcare providers investigating and managing patients with chronic cough. It is important to differentiate productive compared to chronic dry cough. The presence of daily mucus and phlegm should alert the physician to a potentially more serious underlying disorder such as bronchiectasis, uncontrolled asthma, COPD, unresolved pneumonia, or recurrent lower respiratory tract infections due to immunodeficiency. This study also underlines the importance of the American College of Chest Physicians (ACCP) and European Respiratory Society (ERS) guidelines recommending performing a chest X-ray and spirometry in all patients with a chronic cough greater than eight weeks (3,38,39). In secondary care, physicians may consider more detailed testing such as a high-resolution CT (HRCT) scan of the chest, sputum cytology and culture to quantify eosinophils and neutrophils and rule out bacterial, fungal or viral infections. This stratification of productive and dry chronic cough is important for triaging referrals and developing more individualised management pathways for productive and dry chronic cough.

Clinical trials of novel anti-tussives typically require a normal chest X-ray, the absence of airflow obstruction and any serious cardio-pulmonary diseases. Two large 52-week phase 3 studies of gefapixant, a peripherally acting, non-opioid, P2X3 antagonist, demonstrated 45 mg BID reduced objective cough frequency by 15% and 18% over placebo (40). However, most studies on refractory and unexplained chronic cough have yet to provide a detailed clinical description of whether the cough was productive or dry or a sub-group analysis to ascertain if treatment is equally effective in both types of chronic cough. Current sub-group analysis suggests gefapixant is equally effective in refractory and unexplained chronic cough. However, further classification of productive (and, if so, volume) and chronic dry cough would be helpful to clinicians.

There are limitations to this study. First, the CLSA recruited an older population over the age of 45, as the main focus of the study was on aging; hence mortality rates may be higher. Second, acceptable and reproducible pre-bronchodilator spirometry was available only in 22,547 subjects at baseline, and we were unable to confirm airway reversibility or post-bronchodilator airflow obstruction. Third, diagnoses were based on self-reported physician diagnosis, thus possibly resulting in under or over-diagnosis. Fourth, there was missing data in 804 participants who were not seen at follow-up 1, and death could not be confirmed with the Ministry of Health, who were assumed to be alive.

Fifth, we do not have data on the exact cause of death and are unable to differentiate between respiratory and non-respiratory mortality due to chronic cough. Sixth, we were unable to estimate conventional hazard ratios as the exact date of death was unknown.

Conclusions

Chronic productive chronic cough was associated with a higher risk of death after adjusting for potential confounding factors such as age, sex, smoking, BMI and respiratory co-morbidities. This highlights the importance of carefully evaluating, investigating, and monitoring patients presenting with chronic cough.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Hamilton Integrated Research Ethics Board and the CLSA scientific advisory board (Project ID: 1909024) and individual consent for this retrospective analysis was waived.

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